Comparing patient characteristics and outcomes in type 1 versus type 2 diabetes with diabetic ketoacidosis: a review and a propensity-matched nationwide analysis

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ABSTRACT

Diabetic ketoacidosis (DKA) is a known complication of patients with type 1 diabetes mellitus (T1DM), but less common in type 2 diabetes mellitus (T2DM). The aim of this study was to compare the outcomes of patients admitted to the hospital with DKA in T1DM versus T2DM. This was a population-based, retrospective, cohort study using data from the Nationwide Inpatient Sample. The group of patients hospitalized for DKA was divided based on a secondary diagnosis of either T1DM or T2DM. The primary outcome was inpatient mortality, and the secondary outcomes were rate of complications, length of hospital stay (LOS) and total hospital charge (THC). The inpatient mortality for DKA was 0.27% (650 patients). In T2DM, the adjusted OR (aOR) for mortality was 2.13 (95% CI 1.38 to 3.28, p=0.001) with adjusted increase in mean THC of $6035 (95% CI 4420 to 7652, p<0.001) and mean LOS of 0.5 day (95% CI 0.3 to 0.6, p<0.001) compared with T1DM. Patients with T2DM had significantly higher odds of having septic shock (aOR 2.02, 95% CI 1.160 to 3.524, p=0.013) compared with T1DM. T2DM was associated with higher inpatient mortality, septic shock and increase in healthcare utilization costs compared with T1DM.

Significance of this study

What is already known about this subject?
- Diabetic ketoacidosis is an endocrinologic emergency associated with morbidity and mortality.
- Diabetic ketoacidosis is one of the main reasons for admission due to diabetes mellitus.
- The pathophysiology of diabetic ketoacidosis is different depending on the type of diabetes mellitus.

What are the new findings?
- Patients with type 2 diabetes had increase in mortality when matched with similar patients with type 1 diabetes.
- Patients with type 2 diabetes had odds of developing sepsis.
- Patients with type 2 diabetes had longer mean length of hospital stay.

How might these results change the focus of research or clinical practice?
- Increase awareness of diabetic ketoacidosis as an important cause of mortality in patients with type 2 diabetes mellitus.
- Aid development of risk stratification scoring to predict adverse outcomes in patients with type 2 diabetes mellitus who were admitted for diabetic ketoacidosis.

INTRODUCTION

Diabetes mellitus (DM), a disease characterized by hyperglycemia secondary to impaired insulin section, action, or both, is on the rise both in the USA and worldwide. Around the globe, the prevalence of DM across all age groups is projected to reach to about 4.4% by the end of 2030.[1] Diabetic ketoacidosis (DKA) is a metabolic complication which can be seen with both type 1 and type 2 DM (T1DM, T2DM). It is characterized by ketonemia, acidemia, and hyperglycemia; however, hyperglycemia may not always be present.[2] As per numerous population-based studies in the USA, the incidence of DKA has been estimated to be between 4.6 and 8 episodes per 1000 patients with DM. Despite significant improvements in the care for patients with DM over the last few decades and the availability of standardized treatment protocols for these patients, DKA continues to be a life-threatening condition.[3]

Although there exists enormous information in literature on the mechanism and complications of DKA, there is however paucity of information in terms of in-hospital mortality, differences in patient characteristics and the outcomes between T1DM and T2DM. Hence, due to the potential for significant morbidity and mortality, a more in-depth understanding of DKA-related hospitalizations is necessary.

In this study, the Nationwide Inpatient Sample (NIS) database was used to identify the

differences in outcomes for inpatient admissions with DKA based on the type of diabetes (T1DM vs T2DM), identify key differences in mortality, and focus on the characteristics for DKA hospitalizations based on type of DM.

MATERIALS AND METHODS

Design and data source

This was a retrospective cohort study involving adult hospitalizations principally for DKA in the USA between 1 January 2016 and 31 December 2017. Data were sourced from the NIS database for 2016 and 2017. The NIS is a database of hospital inpatient stays derived from billing data submitted by hospitals to state-wide data organizations across the USA, covering more than 97% of the US population.[4] It approximates a 20% stratified sample of discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals. This data set is weighted to obtain national estimates.[5] Both the 2016 and 2017 databases are entirely coded using the International Classification of Diseases, Tenth Revision (ICD-10), Clinical Modification/Procedure Coding System. In the NIS, diagnoses are divided into principal diagnosis and secondary diagnoses. A principal diagnosis was the main ICD-10 code for the hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis.

Study population

Hospitalizations involving patients with a principal discharge diagnosis of DKA were included. This group was stratified with ICD-10 codes into T1DM with DKA and T2DM with DKA (E10.1 and E11.1, respectively). Patients were excluded from the study if they were less than 18 years old, had an unspecified type of DM or had DKA as a secondary diagnosis.

Outcome measures

The primary outcome was comparing inpatient mortality between T1DM and T2DM. Secondary outcomes included rate of sepsis, septic shock, acute kidney failure (AKI), acute respiratory failure (ARF), deep vein thrombosis (DVT), pulmonary embolism (PE), mean length of hospital stay (LOS) and mean total hospital charges (THC).

Statistical analysis

The data were analyzed using Stata V.16 software (StataCorp, Texas, USA). All analyses were conducted using the weighted samples to obtain national estimates. Comorbidity proportions in the studied sample were calculated and χ^2 test was used to compare these characteristics between the patients with T1DM and T2DM. Propensity score matching, probit function, using the kernel matching with replacement was used for analysis of the outcome variables. An initial univariate screen with regression analysis was done to identify confounders. Hospitalizations were matched for age categories, sex, race, household income, hospital region, hospital bed size and grouped Charlson Comorbidity Index (CCI). All p values were two sided, with 0.05 as the threshold for statistical significance.

RESULTS

Patient characteristics

The combined NIS database for 2016 and 2017 contained over 71 million weighted hospital discharges out of which 245,170 met the inclusion criteria for the study. This was divided into 225,495 (92.0%) with T1DM and DKA, and 19,675 (8.0%) with T2DM and DKA.

The patients with a T1DM were significantly younger (mean age 34.4 vs 51.1 years, p<0.001) and had a higher proportion of females in the subgroup (51.5% vs 46.5%, p<0.001) as compared with patients with T2DM. However, patients with T2DM had more comorbidities such as hypertension (45.1% vs 24.5%, p<0.001), congestive heart failure (7.4% vs 3.1%, p<0.001), and chronic kidney disease (10.9% vs 9.1%, p<0.001) compared with those with T1DM. The patient and hospital characteristics are further detailed in table 1.

Primary outcome: in-hospital mortality

The inpatient mortality for DKA was found to be 0.265%. In total, there were 650 deaths in the included hospitalizations for DKA between 2016 and 2017. Patients with T2DM had higher adjusted odds of inpatient mortality (adjusted OR (aOR) 2.09, 95% CI 1.36 to 3.22, p=0.001) when compared with patients with T1DM.

Secondary outcomes

Patients with T2DM had significantly higher odds of having septic shock (aOR 2.02, 95% CI 1.160 to 3.524, p=0.013) compared with T1DM. There was an increase in the mean THC, in US$, in patients with T2DM (3800, 95% CI 1900 to 5700, p<0.001) compared with patients with T1DM. However, there was no statistically significant difference in the mean LOS, and odds of having other complications such as ARF, DVT or PE (table 2).

DISCUSSION

DKA is a metabolic derangement that is commonly seen in patients with DM. The exact prevalence of the condition in the general population is currently unknown. However, the mortality rates have been reported to be as high as 6%–10% thereby indicating the potential seriousness of the diagnosis.[6]

In patients with T1DM, DKA usually manifests after extensive destruction of the β-cell mass of the pancreas and the truly functional β cells are under 10%. The insulin deficit leads to a significant change in the metabolic processes in the adipose tissue, muscle, and the liver.[7] DKA is also seen in patients with T2DM; however, it is commonly associated with an inciting agent which leads to this metabolic derangement. In some cases, the trigger for DKA may be clearly identifiable such as that seen in infections. However, it may also be triggered by discontinuation of certain medications, infarction of the tissue, or other severe illness or stressors.[8]

Although the differences in pathophysiology of DKA in T1DM and T2DM are well known, understanding the key difference in clinical outcomes is of upmost importance. Clinical outcomes may help guide treatment strategies for patients with DKA admitted to the hospital. This study investigated the in-hospital mortality and potential risks for patients with DKA associated with either T1DM or T2DM and yielded several statistically significant results worth delineating.

Table 1 Patient and hospital characteristics of hospitalizations with DKA

Variable	Overall n=245,170	Type 1 DM, % n=225,495 (92.0)	Type 2 DM, % n=19,675 (8.0)	P value
Patient characteristics				
Age, mean (y)		34.4	51.1	<0.001
Women		51.5	46.5	<0.001
Racial distribution				<0.001
White	59.6	60.6	47.4	
Black	23.0	22.5	29.3	
Hispanic	10.2	9.7	15.2	
Others	7.2	7.2	8.1	
Insurance type				<0.001
Medicaid	19.0	17.7	33.9	
Medicare	39.7	40.7	27.6	
Private	28.5	28.8	25.2	
Uninsured	12.8	12.8	13.3	
Charlson Comorbidity Index score				<0.001
1	53.6	54.1	47.2	
2	25.7	25.9	23.4	
≥3	20.7	20.0	29.4	
Median annual income in patient's zip code, US$*				<0.001
1–43,999	38.1	37.7	42.1	
44,000–55,999	27.7	27.9	25.6	
56,000–73,999	21.3	21.4	20.1	
≥74,000	12.9	13.0	12.2	
Comorbidities				
Chronic IHD	7.4	6.8	14.3	<0.001
Hypertension	26.1	24.5	45.1	<0.001
Smoking history	43.0	43.3	39.8	<0.001
CHF	3.4	3.1	7.4	<0.001
CKD	9.3	9.1	10.9	<0.001
Obesity	5.9	4.7	20.1	<0.001
Prior CVA	0.81	0.7	1.9	<0.001
COPD	3.5	3.1	7.5	<0.001
Hospital characteristics				
Hospital region				<0.001
North-east	14.2	14.2	13.8	
Midwest	23.5	23.9	19.0	
South	42.5	42.1	47.6	
West	19.8	19.8	19.6	
Hospital bed size				0.423
Small	21.6	21.6	22.5	
Medium	30.3	30.3	30.8	
Large	48.1	48.1	46.7	
Urban location	87.3	87.2	88.1	0.182
Teaching hospital	61.2	61.0	63.9	0.010

*For 2017.
CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DKA, diabetic ketoacidosis; DM, diabetes mellitus; IHD, ischemic heart disease.

Table 2 Clinical outcomes in hospitalizations for DKA by diabetes type

Outcome	Type 2 DM, %	Type 1 DM, %	aOR (95% CI)	P value*
Primary outcome				
In-hospital mortality	1.04	0.20	2.13 (1.38 to 3.28)	0.001*
Secondary outcomes				
Length of stay, mean (d)	3.7	3.0	0.1 (−0.03 to 0.24)†	0.133
Total hospital charges, mean (US$)	36,600	27,900	3800 (1900 to 5700)†	<0.001*
Sepsis	2.1	1.2	1.24 (0.94 to 1.62)	0.124
Septic shock	0.5	0.2	2.02 (1.16 to 3.52)	0.013*
Acute kidney failure	42.9	33.0	0.92 (0.85 to 0.99)	0.047*
Acute respiratory failure	1.8	1.0	1.06 (0.80 to 1.40)	0.698
Deep vein thrombosis	0.7	0.6	0.91 (0.60 to 1.38)	0.654
Pulmonary embolism	0.2	0.1	1.68 (0.76 to 3.74)	0.202

*Statistically significant.
†Adjusted mean difference.
aOR, adjusted OR; DKA, diabetic ketoacidosis; DM, diabetes mellitus.

Age, gender, and race

The results from the study showed that the average age of patients with DKA admitted to the hospital is over 15 years higher in patients with T2DM versus T1DM (51.1% vs 34.4%, p<0.001). This is likely due to T2DM having higher prevalence in middle age to elderly individuals. Furthermore, the average age at onset in patients with a diagnosis of T2DM was reported to be 46.01 years in the USA.[9] Comparatively, T1DM is a disease that typically presents in childhood (although one-quarter of cases are diagnosed in adulthood). Approximately 80% of the newly diagnosed cases of diabetes in patients aged 19 years and younger in the USA are of T1DM despite the rising prevalence of T2DM among the youth.[10 11] This difference in age of diagnosis or onset may account for the variations in age seen in this study.

The study showed significant gender variation in DKA hospitalization for T1DM and T2DM. With regard to a higher number of women in the T1DM hospitalization group, it is reported that T1DM affects men and women equally.[12] Women, however, are reported to have a 40% greater risk of all-cause mortality as compared with men with T1DM.[13] This higher hospitalization rate in women compared with men may partly explain the overall higher mortality rate reported. With regard to T2DM, it is reported to have a higher prevalence in men than in women secondary to differences in visceral fat deposition and mass in older populations.[14] This higher prevalence may account for the difference in hospitalizations between men and women with T2DM.

Between T1DM and T2DM, there were more whites hospitalized in the T1DM than the T2DM subgroup (60.5% vs 47.4%, p<0.001), whereas T2DM had a greater reporting of a non-white population, namely Blacks (22.5% vs 29.3%, p<0.001) and Hispanics (9.7% vs 15.2%, p<0.001). As per literature, a cross-sectional study that included 7575 adults demonstrated age and sex-adjusted prevalence was as follows: 12.1% for non-Hispanic whites, 20.4% for non-Hispanic blacks, 22.1% for Hispanics, and 19.1% for the non-Hispanic Asian group. The study also reported that undiagnosed and total persons with diabetes were higher in the Hispanic, non-Hispanic black, and non-Hispanic

Asian groups when compared with the non-Hispanic white group. This greater prevalence of both diagnosed and undiagnosed diabetes in the aforementioned groups may have accounted for the higher hospitalization rates in T2DM than T1DM in adults over 20 years of age and the fact that T2DM tends to be diagnosed at a later age than T1DM.[15] In the non-white population, there is a higher reported prevalence of T2DM compared with T1DM, which may have accounted for the greater rates of hospitalization of non-white group compared with the non-Hispanic white groups in this study.[16] Additionally, a higher prevalence of discrepancies in patient education may also exacerbate the problem. The Centers for Medicare & Medicaid Services reported that though Black individuals were just as likely as White individuals to perform self-management activities for their diabetes, they were however less likely to report having adequate knowledge about self-management of their condition. This adds to inadequate glycemic control in these populations. Moreover, it is also reported that fewer Black and Hispanic individuals reported knowing about Medicare coverage policies for diabetic testing supplies and self-management of their T2DM compared with White individuals, which may also account for the greater prevalence of these populations being hospitalized. The differences in self-reported education and management may also account for the differences.

CCI and comorbidities

The CCI was developed to predict the 1-year mortality among the over 600 patients based on the comorbidity data gathered from hospital chart review and weighted based on potential effects on patient mortality.[17] The CCI has been adapted and modified for increased applicability and aids in the prediction of outcomes and risks of mortality with different comorbid diseases.[18] This study reports that scores of 3 or greater for patients were more prevalent in the T2DM than the T1DM group (29.4% vs 20.0%, p<0.001). Older individuals are at a greater risk of developing additional chronic illnesses that would be considered comorbid when compared with their younger counterparts, such as respiratory disease, cancer, cardiovascular problems, and hypertension.[19] This difference in age at diagnosis and associated increase in risk of developing additional comorbid conditions may explain the higher prevalence of CCI scores (≥3) in patients with T2DM than with T1DM hospitalized with DKA. These complications may be due to damage secondary to the aldose reductase-sorbitol or glycation models of glucose-related damage as pathways responsible for the molecular damage seen in patients with DM.[20]

Data also suggest that despite a shorter duration of diabetes in years, there is statistically significant excess in complications with T2DM than in patients with T1DM. Specifically, albuminuria, macrovascular disease and related complications, and ischemic heart disease were reported to be more prevalent in patients with T2DM who were diagnosed at an earlier age than patients with T1DM.[21] Moreover, T2DM is predominantly a disease of insulin resistance rather than deficiency. Both insulin resistance and hyperglycemia are reported to play a significant role in the development of diabetic macroangiopathy, and atherosclerosis secondary to DM.[22] Moreover, diabetic macroangiopathy can cause cerebrovascular accidents which are a source of significant impairment and lowered overall quality of life.[22] Additionally, after adjustments are made for the known risk factors, there is a significantly greater association of microvascular complications in T2DM than T1DM.[23] The literature also points to higher comorbidities and complications in T2DM, although comorbidities are reported frequently in both.[23]

THC, septic shock, and acute kidney failure

T2DM was found to be associated with higher mean THC ($36,600 vs $27,900, p<0.001, aOR 3800 (95% CI 1900 to 5700)), septic shock, and AKI. A possible explanation of the higher THC may be due to the higher incidence of associated comorbidities in patients with T2DM than with T1DM. One study in literature showed that among teenagers and younger adults where a diagnosis of DM was made during childhood or adolescence, there was a higher prevalence of comorbidities and complications among the patients with T2DM compared with T1DM. These complications included kidney disease, retinopathy, hypertension, cardiovascular autonomic neuropathy, peripheral neuropathy, arterial stiffness, and retinopathy.[23] Due to the prevalence of multiple comorbidities, consultation of specialists is warranted, which in part also contributed to increased hospital charges. A higher prevalence of AKI may be associated with an increased risk of septic shock, as the incidence of AKI has been shown to be higher in patients with diabetes with sepsis and septic shock.[24]

Income

Annual incomes under $44,000 were more commonly seen in the T2DM group (T1DM 37.7% vs T2DM 42.1%, p<0.001), whereas the annual incomes of $40,000 or greater were more prevalent in the T1DM group (44,000–55,999: T1DM 27.9% vs 25.6%, p<0.001; >74,000: T1DM 13.0% vs T2DM 12.2%, p<0.001). Therefore, it is often reported that T2DM is more prevalent in lower socioeconomic groups in western societies such as the USA. The conditions implicated with accelerated development of T2DM, such as obesity, physical inactivity or lack of daily exercise, and smoking, are also commonly associated with the lower socioeconomic strata.[25] Additionally, there are theories of psychosocial factors associated with the socioeconomic differences and the risk of developing T2DM such as low sense of coherence, a factor that delineates successful coping with stressors, and low decision latitude at work.[25] The higher prevalence of both psychosocial and non-psychosocial risks associated with T2DM in people of lower socioeconomic status may explain the variance in income and rates of hospitalization between the groups that were studied.

Mortality

Finally, T2DM with DKA was associated with a higher rate of inpatient mortality relative to T1DM (1.04% vs 0.20%, p=0.001, aOR 2.09 (95% CI 1.361 to 3.218)). This increased mortality may be secondary to the differences precipitating events as well as complications in T2DM versus T1DM as explored above.

Strengths and limitations

This study has several strengths, one of which is the study population. The population used for the analysis was drawn from the largest, multiethnic, hospital-based registry in the USA. Additionally, our study also explores numerous demographics and outcome-oriented facets of inpatient admissions of DKA, offering readers a thorough and comprehensive overview of the seriousness of the disease and its burden on the US healthcare system.

Like any study, we also report limitations which include the following: (1) NIS does not contain information on the severity of the disease, and time of diagnosis; (2) data analyzed from NIS are subject to non-randomization associated with retrospective studies; (3) as NIS is an administrative database, it uses ICD-10 codes to obtain relevant hospitalizations and clinical outcomes, and therefore carries a possibility of coding errors; (4) the data obtained from NIS were on DKA hospitalizations rather than individual patients; hence, patients admitted on numerous occasions would be included multiple times in the data set. However, despite these limitations, the large sample size, scientific questions, and analysis technique contribute to a slightly better understanding of a relatively underinvestigated topic, while also aiming to stimulate and encourage further large, controlled, multicenter prospective studies on DKA.

CONCLUSION

DKA is a metabolic derangement that may be a consequence of either T1DM or T2DM. In this study, we observed a higher adjusted odds of inpatient mortality of hospitalized patients with T2DM and DKA. The data also showed higher rates of complications and comorbidities. We strongly believe that patients hospitalized with DKA secondary to underlying T2DM may be at a higher risk of serious complications, including death. Hence, aggressive yet appropriate monitoring for complications should be considered in these hospitalized patients.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The NIS database lacks patient-level identifiers. Since 2012, the NIS has also removed state-level and hospital identifiers. This has enhanced patient protection, privacy, and anonymity. Hence, this study did not require Institutional Review Board approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open-access repository. We used and/or analyzed the NIS database 2016 and 2017, available online at http: //www.hcup- us.ahrq.gov. The NIS is a large publicly available all-payer inpatient care database in the USA, containing data on more than 7 million hospital stays yearly. Its large sample size is ideal for developing national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations.

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